is attached hereto as Exhibit B. A marked up copy of the original title is attached hereto as Exhibit C and clean copy of the amended title is attached hereto as Exhibit D.

II. Support for the Amended Specification and Claims

Claim 1 has been amended to more specifically claim the invention. Amended Claim 1 finds support throughout the specification and Claim 1 as originally filed.

New Claim 11 finds support in original Claim 4, throughout the specification as originally filed with particular support being found at least on page 13, lines 25-32.

New Claim 12 finds support throughout the specification as originally filed with particular support being found at least on page 13, lines 25- page 14, line 1.

As the amendments to Claim 1 and new claims 11 and 12 are fully supported by the specification and claims as originally filed, they do not constitute new matter. Entry therefore is respectfully requested.

III. Objection

The Action objects to the title of the disclosure because it allegedly is not descriptive for use of the term "Novel". Applicants in no way agree, however, in order to progress the application more rapidly towards allowance Applicants have amended the title to remove the term.

IV. Rejection of Claims 1-4 Under 35 U.S.C. § 112, First Paragraph

The Action next rejects claims 1-4 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not disclosed in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Action rejects Claim 1 because allegedly it encompasses subject matter that is not defined in the specification.

35 U.S.C. § 112, first paragraph, requires that the specification contain a written description of the invention. The Federal Circuit in *Vas-Cath Inc. v. Mahurkar* (19 USPQ2d 1111 (Fed. Cir.

1991); "*Vas-Cath*") held that an "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*." *Vas-Cath*, at 1117, emphasis in original. However, it is important to note that the above finding uses the terms reasonable clarity to those skilled in the art. Further, the Federal Circuit in *In re Gosteli* (10 USPQ2d 1614 (Fed. Cir. 1989); "*Gosteli*") held:

> Although [the applicant] does not have to describe exactly the subject matter claimed, ... the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.

Gosteli at 1618, emphasis added. Additionally, *Utter v. Hiraga* (6 USPQ2d 1709 (Fed. Cir. 1988); "*Utter*"), held "(a) specification may, within the meaning of 35 U.S.C. § 112 ¶1, contain a written description of a broadly claimed invention without describing all species that claim encompasses" (*Utter*, at 1714). Therefore, all Applicants must do to comply with 35 U.S.C. § 112, first paragraph, is to convey the invention with reasonable clarity to the skilled artisan.

Further, the Federal Circuit has held that an adequate description of a chemical genus "requires a precise definition, such as by structure, formula, chemical name or physical properties" sufficient to distinguish the genus from other materials. *Fiers v. Sugano*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993; "*Fiers*"). *Fiers* goes on to hold that the "application satisfies the written description requirement since it sets forth the ... nucleotide sequence" (*Fiers* at 1607). In other words, provision of a structure and formula - the nucleotide sequence - renders the application in compliance with 35 U.S.C. § 112, first paragraph.

More recently, the standard for complying with the written description requirement in claims involving chemical materials has been explicitly set forth by the Federal Circuit:

> In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus. *Univ. of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Thus, a claim describing a genus of nucleic acids by structure, formula, chemical name or physical properties sufficient to allow one of ordinary skill in the art to distinguish the genus from other materials meets the written description requirement of 35 U.S.C. § 112, first paragraph. As further elaborated by the Federal Circuit in *Univ. of California v. Eli Lilly and Co.*:

> In claims to genetic material ... a generic statement such as 'vertebrate insulin cDNA' or 'mammalian insulin cDNA', without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art cannot, as one can do with a fully described genus, visualize or recognize the identity of members of the genus. (Emphasis added)

Thus, as opposed to the situation set forth in *Univ. of California v. Eli Lilly and Co.* and *Fiers*, the nucleic acid sequences of the present invention are not distinguished on the basis of function, or a method of isolation, but in fact are distinguished by structural features - a chemical formula, *i.e.*, the *sequence itself.*

Using the nucleic acid sequences of the present invention (as set forth in the Sequence Listing), the skilled artisan would readily be able to distinguish the claimed nucleic acids from other materials on the basis of the specific structural description provided. Polynucleotides comprising the nucleotide sequence of , for example, SEQ ID NO:1 or a nucleotide sequence that encodes SEQ ID NO:2, are within the genus of the instant claims, while those that lack this structural feature lie outside the genus. Thus those of skill in the art would have known how to make and use the invention as claimed in original Claim 1. Again, **however**, Applicants respectfully submit that as Claim 1 has been revised to read on the full-length sequence of SEQ ID NO: 1 this issue has been rendered moot.

The Action also rejects Claim 2 due to lack of written description. Applicants respectfully invite the Examiner's attention to the fact that Claim 2, reads on an isolated nucleic acid molecule comprising a nucleotide sequence that: (a) encodes the amino acid sequence shown in SEQ ID NO: 2; and (b) hybridizes under highly stringent conditions to the nucleotide sequence of SEQ ID NO: 1 or

the complement thereof. As such, Claim 2 has two limitations. The isolated nucleic acid must encode the amino acid sequence of SEQ ID NO: 2 and it must hybridize under highly stringent conditions to the nucleotide sequence of SEQ ID NO: 1 or the complement thereof. This is finite and well defined group, which those of skill in the art could easily identify and would know how to make and use. Applicants respectfully submit that the breadth of Claim 2 is clearly defined and is not excessive and that the skilled artisan would know how to make and use the claimed molecules. Therefore, Applicants respectfully request that rejection of Claim 2 under 35 U.S.C. § 112, first paragraph, be withdrawn.

V. Rejection of Claim 1 Under 35 U.S.C. § 112, Second Paragraph

The Action next rejects Claim 1 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully submit that revision of Claim 1 to read on to read on the full-length sequence of SEQ ID NO: 1 this issue has been rendered moot. Applicants submit that rejection of Claim 1 under 35 U.S.C. § 112, second paragraph has been avoided and respectfully request withdrawal.

VI. Rejection of Claims 1-4 Under 35 U.S.C. § 101

The Action next rejects claims 1-4 under 35 U.S.C. § 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility. Because the present application describes splice variants of human semaphorin, a molecule whose activity and utility is known to the art , Applicants respectfully traverse.

As set forth by the Federal Circuit, "(t)he threshold of utility is not high: An invention is 'useful' under section 101 if it is capable of providing some identifiable benefit." *Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700 (Fed. Cir. 1999) (citing *Brenner v. Manson*, 383 U.S. 519, 534 (1966)). Additionally, the Federal Circuit has stated that to violate § 101 the claimed invention "must be totally incapable of achieving a useful result." *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992), emphasis added. *Cross v. Iizuka* (224 USPQ 739 (Fed. Cir. 1985)) states "any utility of the claimed compounds is sufficient to satisfy 35 U.S.C. § 101". *Id* at 748, emphasis added. Indeed, the Federal Circuit recently emphatically confirmed that "anything under the

sun that is made by man" is patentable *(State Street Bank & Trust Co. v. Signature Financial Group Inc.*, 47 USPQ2d 1596, 1600 (Fed. Cir. 1998), citing the U.S. Supreme Court's decision in *Diamond vs. Chakrabarty*, 206 USPQ 193 (S.Ct. 1980)).

As the protein of the instant invention represents a variant of human hemicentin, a molecule with a common, well established specific and substantial utility, the Federal Circuit's ruling in *In re Brana,* (34 USPQ2d 1436 (Fed. Cir. 1995), "*Brana*") is completely on point. In *Brana*, the Federal Circuit admonished the P.T.O. for confusing "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption". *Brana* at 1442. The Federal Circuit went on to state:

> At issue in this case is an important question of the legal constraints on patent office examination practice and policy. The question is, with regard to pharmaceutical inventions, what must the applicant provide regarding the practical utility or usefulness of the invention for which patent protection is sought. This is not a new issue; it is one which we would have thought had been settled by case law years ago.

Brana at 1439, emphasis added. The choice of the phrase "utility or usefulness" in the foregoing quotation is highly pertinent. The Federal Circuit is evidently using "utility" to refer to rejections under 35 U.S.C. § 101, and is using "usefulness" to refer to rejections under 35 U.S.C. § 112, first paragraph. This is made evident in the continuing text in *Brana*, which explains the correlation between 35 U.S.C. §§ 101 and 112, first paragraph. The Federal Circuit concluded:

> FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

Brana at 1442-1443, citations omitted.

Thus the legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible or believable. According to the Examination Guidelines for the Utility Requirement, if the applicant has asserted that the claimed

invention is useful for any particular purpose (i.e., it has a "specific and substantial utility") and the assertion would be considered credible by a person of ordinary skill in the art, the Examiner should not impose a rejection based on lack of utility (66 Federal Register 1098, January 5, 2001).

As evidence of the credibility of Applicants assertion that the present invention is a variant of human semaphorin, Applicants submit an amino acid sequence comparison between SEQ ID NO: 3 and BAA98132 (**Exhibit E**), which have been annotated by third party scientists, wholly unaffiliated with Applicants, as encoding semaphorin sem2 [Homo sapiens] (BAA98132: **Exhibit F**). It is also clear that SEQ ID NO: 1 (see **Exhibit G** comparing SEQ ID NOS: 3 and 1) identifies a longer isoform of the present invention, which is clearly encoded by the same genetic locus. Clearly those of skill in the art would recognize the sequences of the present invention as encoding a human semaphorin. As evidenced by the review article entitled "Molecular Mechanisms of Axonal Guidance" from the prestigious journal Science (298:1959-1964, 2002 and erratum; **Exhibit H**), semaphorins are well known to those of skill in the art as soluble and membrane-bound proteins that act as chemorepulsive factors in neuronal development, thereby playing a crucial role in axon guidance. Semaphorins, such as the one described in the present invention, provide guidance for neuronal growth. In the second paragraph of section 5.1 or the specification as filed, it is stated that "Because of their role in neural development, semaphorins have been subject to considerable scientific scrutiny. For example, U.S. Patents Nos. 5,981,222 and 5,935,865, both of which are herein incorporated by reference, describe other semaphorins as well as applications, utilities". Therefore, clearly, there can be no question that Applicants' asserted identity and utility for the described sequences a semaphorin is "credible." In addition, those of skill in the art in the biomedical and pharmaceutical industry would readily recognize the utility for semaphorins and their application to medical conditions requiring nerve regeneration. For example, the regeneration and repair of nerve tissue following the surgical attachment of severed limbs or the resection of diseased tissue, as well as nerve repair following a stroke.

Applicants have thus supplied evidence supporting their assertion that those of skill in the art would recognize that the sequences of the present invention encode variants of human semaphorin. Applicant's assertion also supports a "well-established" utility in that persons of ordinary skill in the art would immediately appreciate. In contrast, the Examiner has provided no evidence of record indicating that those of skill in the art would not recognize the sequences of the present invention encode

semaphorin. As such, the scientific evidence clearly establishes that Applicants have described an invention whose utility is in full compliance with the provisions of 35 U.S.C. § 101, and therefore Applicants respectfully request withdrawal of the rejection.

Applicants note that even if, *arguendo*, further research might be required in certain aspects of the present invention, this does not preclude a finding that the invention has utility, as set forth by the Federal Circuit's holding in *Brana*, which clearly states, as highlighted in the quote above, that "pharmaceutical inventions, necessarily includes the expectation of further research and development" (*Brana* at 1442-1443, emphasis added). In assessing the question of whether undue experimentation would be required in order to practice the claimed invention, the key term is "undue", not "experimentation". *In re Angstadt and Griffin*, 190 USPQ 214 (CCPA 1976). The need for some experimentation does not render the claimed invention unpatentable. Indeed, a considerable amount of experimentation may be permissible if such experimentation is routinely practiced in the art. *In re Angstadt and Griffin, supra*; *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). As a matter of law, it is well settled that a patent need not disclose what is well known in the art. *In re Wands*, 8 USPQ 2d 1400 (Fed. Cir. 1988).

As just one example of utility of the present nucleotide sequences, Applicants point out that, as taught in the specification as originally filed the claimed polynucleotide sequences can be used to track the expression of the genes encoding the described proteins. In particular, the specification describes how the described sequences can be represented using a gene chip format to provide a high throughput analysis of the level of gene expression. Such "DNA chips" clearly have utility, as evidenced by hundreds of issued U.S. Patents, as exemplified by U.S. Patent Nos. 5,445,934, 5,556,752, 5,744,305, 5,837,832, 6,156,501 and 6,261,776. Evidence of the "real world" substantial utility of the present invention is provided by the fact that there is an entire industry established based on the use of gene sequences or fragments thereof in a gene chip format. Perhaps the most notable gene chip company is Affymetrix. However, there are many companies which have, at one time or another, concentrated on the use of gene sequences or fragments, in gene chip and non-gene chip formats, for example: Agilent Technologies, Gene Logic, ABI-Perkin-Elmer, HySeq and Incyte. In addition, one such company, Rosetta Inpharmatics, was viewed to have such "real world" value (net equity value of the transaction was $620 million) that it was acquired by large pharmaceutical company, Merck &

Co., for significant sums of money. The "real world" substantial industrial utility of gene sequences or fragments would, therefore, appear to be widespread and well established. The sequences of the present invention describe a novel human semaphorin and thus provide a unique identifiers of human semaphorin. Such gene chips clearly have utility, as evidenced by hundreds of issued U.S. Patents, such as U.S. Patent Nos. 5,445,934, 5,556,752, 5,744,305, 5,837,832, 6,156,501 and 6,261,776. The present nucleotide sequences clearly encode variants of human semaphorin, as detailed throughout the specification. Therefore, as the present sequences are specific markers of the human genome, and such specific markers are targets for the discovery of drugs that are associated with human disease, those of skill in the art would instantly recognize that the present nucleotide sequences would be an ideal, novel candidate for assessing gene expression using such gene chips. Clearly, compositions that enhance the utility of such DNA chips, such as the presently claimed nucleotide sequences, must in themselves be useful. Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Although Applicants need only make one credible assertion of utility to meet the requirements of 35 U.S.C. § 101 (*Raytheon v. Roper*, 220 USPQ 592 (Fed. Cir. 1983); *In re Gottlieb*, 140 USPQ 665 (CCPA 1964); *In re Malachowski*, 189 USPQ 432 (CCPA 1976); *Hoffman v. Klaus*, 9 USPQ2d 1657 (Bd. Pat. App. & Inter. 1988)), as a further example of the utility of the presently claimed polynucleotides, the Examiner is respectfully reminded that only a minor percentage of the genome actually encodes exons, which in-turn encode amino acid sequences. The presently claimed polynucleotide sequences provide biologically validated empirical data (*e.g.*, showing which sequences are transcribed, spliced, and polyadenylated) that *specifically* define that portion of the corresponding genomic locus that actually encodes exon sequence. Equally significant is that the claimed polynucleotide sequences define how the encoded exons are actually spliced together to produce an active transcript (*i.e.*, the described sequences are useful for functionally defining exon splice-junctions). The Applicants respectfully submit that the practical scientific value of expressed, spliced, and polyadenylated mRNA sequences is readily apparent to those skilled in the relevant biological and biochemical arts. For further evidence in support of the Applicants' position, the Examiner is requested to review, for example, section 3 of the Venter *et al.* article (Science, 2001, *291*:1304 *at* pp. 1317-1321, including Fig. 11 at pp.1324-1325), which demonstrates the significance of expressed sequence information in the structural analysis of genomic data. The presently claimed polynucleotide sequences

define biologically validated sequences that provide a unique and specific resource for mapping genome essentially as described in the Venter *et al.* article Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Furthermore, persons of skill in the art, as well as thousands of venture capitalists and investors, readily recognize the utility, both scientific and commercial, of genomic data in general, and specifically human genomic data. Billions of dollars have been invested in the human genome project, resulting in useful genomic data (see, *e.g.*, Venter *et al.*, 2001, Science *291*:1304). The results have been a stunning success, as the utility of human genomic data has been widely recognized as a great gift to humanity (see, *e.g.*, Jasny and Kennedy, 2001, Science *291*:1153). Clearly, the usefulness of human genomic data, such as the presently claimed nucleic acid molecules, is substantial and credible (worthy of billions of dollars and the creation of numerous companies focused on such information) and well-established (the utility of human genomic information has been clearly understood for many years).

Finally, Applicants respectfully submit that polymorphisms identified in the sequences of the present invention (Section 5.1) provide significant and specific utility as taught in the specification. Such polymorphisms have significant and specific utility in, *intra alia*, the fields of forensic science and human population biology. Such polymorphisms can also be used as specific markers useful, for example, in identifying human remains, determining human group migration patterns by identifying descendants of a specific group and in addition clearly the polymorphism of the present invention has significant and specific utility in resolving issues of paternity. Further, Applicants submit that these utilities are not only credible, but well established and known to those of skill in the art. As such polymorphisms are the basis for forensic analysis, paternity identification and population biology studies, which are undoubtedly "real world" utilities, utilities for which identified polymorhisms, such as that provided are utilized daily by those of skill in the art. Therefore, the present sequences logically must in themselves be useful. In and of themselves each of these polymorphisms, including silent ones, has significant and specific utility, the specificity of this utility is only amplified by the presence of more than one polymorphism which can arise in various combinations. It is also important to note that the presence of more useful polymorphic markers for such analysis would not mean that the present sequences lack utility.

Therefore, given not only the preponderance of the evidence but for each of the foregoing reasons, and because it is clear that it has been established that it is far more likely than not that a

person skilled in the art would consider credible the utilities asserted by the applicant for the claimed invention, Applicants submit that the rejection of the claims under 35 U.S.C. § 101 have been overcome, and respectfully request that the rejection be withdrawn.

VII. Rejection of Claims 1-4 1 Under 35 U.S.C. § 112, First Paragraph

The Action next rejects claims 1-4 under 35 U.S.C. § 112, first paragraph specifically since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. Applicants respectfully traverse.

Applicants submit that all claims have been shown to have "a specific, substantial, and credible utility", as detailed above. Applicants therefore request that the rejection of all claims under 35 U.S.C. § 112, first paragraph, be withdrawn.

VIII. Conclusion

The present document is a full and complete response to the Action. In conclusion, Applicants submit that, in light of the foregoing remarks, the present case is in condition for allowance, and such favorable action is respectfully requested. Should Examiner Chism have any questions or comments, or believe that certain amendments of the claims might serve to improve their clarity, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,

February 12, 2003
Date

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